

the palatal material insufficiency, prompted us to identify molecules that, in addition to the mechanical stimuli from the musculature, may be instructing the palatal shelves to fuse. To that end, we employed cDNA microarray analysis comparing the normal palate to the cleft palate in muscleless mouse fetuses. Using a minimum difference of 3.5, we obtained 19 up-regulated and 115 down-regulated molecules. Our consultation of expression, distribution and function databases revealed the following candidate molecules with a novel function in the palatal development: Tgfb2, Bmp7, Gdf11, Trim71 and possibly E2f5, Ddx5, Gfap and Sema3f. Currently, we are completing our analysis of Gdf11 mice that clearly shows cleft palate. This work is funded by NSERC, CFI and DMRF to B.K.

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#### Program/Abstract # 404

##### **Resveratrol prevents impairment in MAP kinase pathways and protects the embryos against malformations in a rodent model of diabetic embryopathy**

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Diabetes is a metabolic disorder known to induce various complications in the eye, kidney, peripheral and central nervous system. In case of females the problem gets further aggravated as diabetes also impairs embryonic development during pregnancy and causes diabetic embryopathy. The high rate of birth defects associated with diabetic embryopathy is a significant public health problem in United States. Among the various malformations in diabetic embryopathy, neural tube defects (NTDs) are the most common complications. Many studies have shown that 50–70% of NTDs can be prevented by folic acid supplementation before and during pregnancy. However, complete protection by any drug or supplementation remains elusive. G-proteins (Gi/Go/Gz) have been reported to be involved in neural tube closing and knocking out of Rho GTPase (Rac1) causes exencephaly and spina bifida. Recent studies suggest that resveratrol improves insulin sensitivity, lowers plasma glucose, and increases mitochondrial capacity in diet-induced obese mice. This study investigated if resveratrol prevents diabetes-induced embryonic malformations. Using a rodent model of diabetic embryopathy we demonstrate that resveratrol (100 mg/kg body wt) administration to diabetic dams reduces blood sugar and improves lipid profile (Singh et al., *Mol Nutr Food Res* 2011, 55: 1–11). It also prevents malformations such as NTDs in the embryos. Our immunohistology and biochemical assays further show that diabetes affects MAP kinase pathways while resveratrol prevents it. As MAP kinase pathways are also regulated by Rho GTPases (RhoA and Rac1), resveratrol may target Rho GTPase signaling to prevent neural tube defects.

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#### Program/Abstract # 405

##### **High concentrations of peroxynitrite in sperm induce infertility on spontaneously diabetic rat models**

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One of the common causes of infertility is the defective sperm function. Sperm can produce both  $O_2^{\cdot-}$  and NO during capacitation, and these two radicals combine to form peroxynitrite ( $ONOO^{\cdot-}$ ). Tyrosine nitration is a generally used marker of  $ONOO^{\cdot-}$ .  $ONOO^{\cdot-}$  has a very short half-life, but it is able to make selective protein 3-

nitrotyrosine (on sperm protein), so 3-NT is measured as pointer for the formation of  $ONOO^{\cdot-}$ . Meanwhile oxidative stress (especially  $ONOO^{\cdot-}$ -mediated) has been considered to be pathogenesis of diabetic complications. Some studies have shown that the level of NT was significantly increased in plasma of diabetic rat, compared with control rats. It means that overproduction of  $ONOO^{\cdot-}$  had an effect on diabetes. Also other studies revealed the involvement of NT during the sperm capacitation and acrosome reaction. Therefore, this report aimed to clarify the effect of  $ONOO^{\cdot-}$  on sperm function impairment in spontaneously diabetic rat models. We evaluated physiological effect of  $ONOO^{\cdot-}$  on these rat sperm function and compared Sprague-Dawley (SD) rats. For NT protein expression level evaluation, we used western blotting analysis. Level of 3-NT-containing proteins in spontaneously diabetic rats was significantly increased than SD. Moreover, we examined the change of sperm motility and capacitation, and our work indicates that excessive exposure of spontaneously diabetic rats sperm to  $ONOO^{\cdot-}$  decreases motility and capacitation. This result demonstrates that induced sperm dysfunction by overproduction of  $ONOO^{\cdot-}$  have a potential pathogenic role in infertility of diabetes.

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#### Program/Abstract # 406

##### **The role of folic acid in regulating epigenetic processes during mammalian embryonic development**

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Gene-environment interactions influence embryonic development and diseases. Folic acid (FA) supplementation is used as a public health measure for prevention of birth defects. How FA interacts with genetic components during embryogenesis remains poorly defined mainly due to our inability to study FA-gene interactions in human development. Here, we utilize the power of mouse genetics and embryology to study the molecular interaction between FA and the Line 3 Poly (L3P) genetic component in mice. Under multi-generational low (2 ppm) FA diet, heterozygous females harboring L3P mutation undergo embryonic lethality. Importantly, L3P± lethality is rescued under high (10 ppm) FA diet. We hypothesize that L3P± female loss is due to defects in the maintenance of the inactivated X chromosome (Xi). As FA is a methyl donor for DNA methylation and DNA methylation is essential for Xi maintenance, FA may rescue Xi maintenance defects through the DNA methylation pathway. Here, we will define when L3P± females are lost and if Xi maintenance defects underlie L3P± female loss. Furthermore, we will examine if FA rescues Xi maintenance defects in L3P± females and identify the L3P genetic component. In addition, we will identify genes downstream of L3P genetic component and FA pathway. Finally, we will examine the epigenetic changes that result from a multi-generational FA diet. Together, these studies will provide insights into the molecular mechanisms by which FA influences epigenetic processes during mammalian development. These studies are of relevance to human health considering US population-wide grain fortification with FA and maternal periconceptional use of FA to decrease the risks of birth defects.

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#### Program/Abstract # 407

##### **Sprouty loss of function mutations in the mouse results in defects characteristic of 22q11 deletion syndrome, which are exacerbated by Tbx1 haploinsufficiency**

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